The Annals of Clinical and Analytical Medicine
Original Research

Vitamin D status and association with disease activity and quality of life in patients with rheumatoid arthritis

Senem Şaş[1], Fatmanur Aybala Koçak[2], Emine Eda Kurt[2], Hatice Rana Erdem2· Figen Tuncay[2]
[1]Department of Physical Medicine and Rehabilitation Ahi Evran University Training and Research Hospital,
[2]Department of Physical Medicine and Rehabilitation, Ahi Evran University School of Medicine, Kırşehir, Turkey

Abstract

Aim: The aim of this study is to determine the vitamin D level in patients with RA (Rheumatoid Arthritis) and association with clinic and laboratory parameters and quality of life. Material and Method: Out of 111 patients with RA and 107 healthy controls who were admitted to Ahi Evran University Training and Research Hospital were included in this study. Patients underwent clinical, laboratory, functional, and quality of life examination. Laboratory tests used for patient evaluations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP). Disease activity was calculated by DAS28 (Disease Activity Score) and functional and quality of life was examined by RAQoL (Rheumatoid Arthritis Quality of Life), HAQ (Health Assessment Questionnaire). Larsen score was calculated to assess the radiographic damage. Results: There was no significant difference between the patient and control groups regarding age, sex and vitamin D level ($p > 0.05$). There were no correlation between vitamin D and Larsen score, RAQoL, HAQ, ESR, and CRP ($p > 0,05$). We found negative correlation between DAS28 (Disease Activity Score) and vitamin D ($r = -0,416$, $p = 0,014$). We found negative correlation between morning stiffness and vitamin D ($r = -0,454$, $p = 0,007$).

Patients with RA were divided into two groups with D vitamin deficiency (0-19 ng / mL) and vitamin D (> 20 ng / mL). There was a negative correlation with morning stiffness in the group with vitamin D deficiency ($r = -0,454$, $p = 0,007$). There was a negative correlation between DAS28 score and vitamin D deficiency ($r = -0.416$, $p = 0.014$). Discussion: This study presents a negative correlation between serum vitamin D level and DAS28. Since vitamin D has autoimmune roles, deficiency or inadequacy can cause flaring in patients with RA. In the light of these findings, we recommend vitamin D supplementation.

Keywords

Rheumatoid Arthritis; Vitamin D; Disease Activity; Deficiency; Autoimmune Role

DOI:10.4328/ACAM.5967 Received: 15.07.2018 Accepted: 28.08.2018 Published Online: 05.09.2018 Printed: 01.07.2019 Ann Clin Anal Med 2019;10(4): 462-5
Corresponding Author: Senem Şaş, Department of Physical Medicine and Rehabilitation, Ahi Evran University Training and Research Hospital, Kirsehir, Turkey.
T.: +90 3862134515-1169 GSM: +905055520451 E-Mail: senemsas@gmail.com
ORCID ID: https://orcid.org/ 0000-0002-5616-5723

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoinflammatory disease that involves predominantly joints. The typical course of the disease presents synovial inflammation, cartilage damage and bone resorption [1]. The pathogenesis of RA is not still fully understood but some susceptibility factors may include genetic factors, environmental triggers, and activation of the acquired and natural immunity [2].

Vitamin D is a hormone that plays a major role in regulation of bone metabolism and its insufficiency causes rickets in children and osteomalacia in adults. The 25-hydroxy-vitamin D (25-OH-D) has been mentioned to inhibit T-cell expansion and down-regulate inflammatory cytokines and 1,25-dihydroxy vitamin D3 [1,25 (OH)2D3] discourage IFN-γ and IL-12 secretion [2,3]. Data indicate that sufficient vitamin D levels have a protective role against autoimmunity through inhibiting T cell expansion and inflammatory mediators in inflammatory rheumatic diseases including RA [4-6].

Also, some studies reported the association between seasonal variations in serum levels of vitamin D, disease activity and latitude in patients with RA [7,8]. Furthermore, it has been showed increasing vitamin D had no association to relative risk of developing RA [10]. However, contradictory results have been published in the literature about vitamin D and RA activity [7-24]. It has been reported that vitamin D has a negative correlation between DAS28, CRP and HAQ values [25]

Therefore, the aim of the present study was to evaluate the vitamin D level in patients with RA and association with clinic and laboratory parameters and quality of life.

Material and Method

Patients

Out of 111 patients (aged between 30 and 84 years) with RA and 107 healthy controls who were admitted to Ahi Evran University Training and Research Hospital were included in this study.

The inclusion criteria were to be a volunteer patient with a rheumatoid arthritis disease. Exclusion criteria were the presence of chronic medical disorders requiring medical treatments, fractures, infectious diseases, malignant tumors, unstable hypertension, severe cardiovascular problems, major hepatic and renal insufficiency, hemorrhagic diseases, serious anemia, pregnancy, psychiatric disorder, and systemic inflammatory disease except RA.

All the patients were diagnosed by the same physician (SS) at the Physical Medicine and Rehabilitation clinic. Laboratory tests used for patient evaluations included complete blood count, erythrocyte sedimentation rate, C-reactive protein level, fasting blood glucose level, hepatic and renal function tests, rheumatoid factor, and thyroid function tests. The patients who met the inclusion and exclusion criteria were admitted to the hospital outpatient clinic.

The patients were fully informed about the nature and purpose of the study. Written informed consents were obtained. The study was approved by the ethics committee (Approval number: 2017-04/31).

Outcome Measures

Demographic and clinical features and measurements were performed before participation. Patient data, included age, gender, smoking history, disease duration, health assessment questionnaire (HAQ), Rheumatoid arthritis quality of life (RAQoL), disease activity score (DAS28), Larsen score, Hemoglobin, platelet, white blood cell, rheumatoid factor, sedimentation (ESR), C-Reactive protein (CRP), serum vitamin D level, number of tender joints, number of swelling joints.

Disease activity was examined by disease activity score (DAS28) including 28 joints, ESR, patient VAS (visual analogue scale) (0-100), where 0 = best and 100 = worst, and both swollen and tender joint number. DAS28 scores is defined high (> 5,1), moderate (3,2 < 5,1) and slightly active disease (≤ 3,2) respectively [26]. It is calculated as follows:

DAS28 (ESR) = 0.56*!(TJC28) + 0.28*!(SJC28) + 0.014*GH + 0.70*ln (ESR)

TJC = tender joint count and SJC = swollen joint count.

Larsen score was analyzed by the same physician from hand radiography. Wrist, 2-5 proximal interphalangeal and 2-5 metacarpophalangeal joint were assessed. Radiography was scored 0 to 5 points, where 0 = no abnormalities, 1 = slight abnormalities, 2 = small but define erosions, 3 = medium erosions, 4 = severe destructive abnormalities, 5 = mutilating abnormalities [27].

Health status was measured by HAQ. HAQ includes 20 activities of daily living with four answers (0 = any difficulty, 1 = some difficulty, 3 = much difficulty, 4 = inability) were classified into eight groups. The score is assigned to the highest point in each group. Patients were asked to use any device or aids, or help from another person [28].

Life quality was assessed by RAQoL in patients with Rheumatoid arthritis. RAQoL was formed of 30 items with a yes/no (1/0) response [29].

All the measurements were taken by the same physician. All patients received medical immunosuppressive treatment. The patients did not receive vitamin D supplementation.

Statistical analyses

Descriptive statistical methods including frequency distribution tables, graphs, central and distribution tendencies were utilized to analyze the data. Kolmogorov-Smirnov test was utilized to check the normality of data distribution. Comparing the qualitative values of the two groups was carried out using independent-samples t-test or its non-parametric equivalent. Chi-square test was employed to examine the relationship between qualitative variables. The significance level was defined at $p < 0.05$. Data analysis was performed using SPSS version 20.0 Software.

Results

The demographic features of the patient and control group were displayed in Table 1. There was no significant difference between the patient and control groups regarding age, sex and vitamin D level ($p > 0.05$). There was no correlation between vitamin D level and Larsen score, RAQoL, HAQ, ESR and CRP ($p > 0,05$). The negative correlation was found between DAS28 and vitamin D level ($r = -0,416$, $p = 0,014$). We found negative correlation between morning stiffness and vitamin D ($r = -0,454$,

p = 0,007).

Patients with RA were divided into two groups with D vitamin deficiency (0-19 ng / mL) (n = 34) and D vitamin (> 20 ng / mL). There was a negative correlation with morning stiffness in the group with vitamin D deficiency (r = -0,454, p = 0,007) and a negative correlation between DAS28 score and D vitamin deficiency (r = -0.416, p = 0.014).

Table 1. Demographic features of Rheumatoid Arthritis and Healthy Control

	RA (n=111)	Control (n=107)	p
Female	84 (%75.7)	82(%76.6)	
Male	27(%24.3)	25(%23.4)	0,1320
Age	56,96±12,40	56,67±11,95	0,908
Disease duration (years)	8,48±8,89		
Morning stiffness (minutes)	22,93±24,32		
VAS (0-10)	4,76±2,53		
Patient Global Assessment	4.76±2,49		
Doctor Global Assessment	4,71±2,49		
Das28	3,56±1,43		
Hgb (12.6-17.4 g/dL)	13,10±1,63		
Plt (130-450 10^3/uL)	290,76±99,34		
WBC(4- 10.2 10^3)	7,18±2,49		
RF (0-14 IU/mL)	73,53±136,96		
ESR (mm/h)	22,77±18,36		
RAQoL (0-30)	9,95±6,49		
CRP (0,015-0,50 mg/dL)	1,15±3,12		
Vitamin D (20-60 ng/mL)	24,93±15,08	26,37±18,33	0,973
Larsen score	15,60±18,92		
Number of swelling joint	1,84±3,33		
Number of tender joints	4,84±4,95		
HAQ score	1,07±0,58		

Discussion

This study investigated vitamin D level and association with disease activity and quality of life in patients with RA and healthy controls. The results indicated that there is no significant difference in vitamin D levels in patients with RA compared with healthy controls. And also in the RA group, there was a negative correlation between DAS-28 and morning stiffness. This negative correlation also persisted when vitamin D was lower than 20 ng / mL. But we didn't note any correlation between acute-phase reactants, life quality scales, number of tender joints, number of swollen joints, disease duration, patient, and doctor global assessment and hemogram parameters. Patients with RA were not under vitamin D supplementation.

Vitamin D deficiency is a widespread health condition. It has been recommended, as a routine procedure for measuring serum vitamin D level in patients with RA. It has been estimated that 25 (OH) D level of above 30 ng/mL (75nmol/L) is optimal by various groups including Endocrine Society [30].

It was published that more vitamin D intake reduces the prevalence of RA in Northern Europe compared with Southern Europe [7]. Also, a report including data of 15 different countries confirms variation of serum D vitamin levels [31]. This difference is explained due to the differences in people such as ethnic variation, climate, sun exposure, dressing style or latitude [7, 31]. Since this study was performed in a rural area of Turkey, ethnic variations were not noted.

Turhanoglu et al. reported that there is a negative correlation between DAS28 and vitamin D. They also found that there is no difference in vitamin D levels in RA and healthy controls. Serum 25-OH vitamin D levels were correlated inversely with DAS28, CRP, and HAQ [25]. We didn't find any correlation with vitamin D and health status, health quality, and acute phase reactants. Similar to this study, there was no difference between the patient and the control group.

Comparable results have been demonstrated by various studies [7-24]. Besides, Cutolo et al. reported a negative correlation between vitamin D and RA disease activity showing a circadian rhythm [8].

Contradictory results were also published. Baker et al. and Feser et al. reported that there is no correlation between serum vitamin D level and RA disease activity [10, 32]. Furthermore, Saseli et al. found non-significant improvement in the effect of oral vitamin D supplementation in active RA patients receiving methotrexate treatment [33]. Our study results suggest vitamin D intake to improve the DAS28 score. All patients were taking immunosuppressive treatment.

The progress of RA is influenced by various environmental and genetic factors. Actually, it has been shown in murine models that vitamin D may suppress incidence and development of collagen-induced arthritis [34]. Furthermore, vitamin D receptor (VDR) agonists may prevent collagen-induced arthritis [35]. VDR gene polymorphism can affect serum vitamin D levels and function and RA development [36]. VDR is found at high levels in immune system cells such as dendritic cells, macrophages and activated T and B lymphocytes [37]. Vitamin D prevents inflammatory process by adaptive immune responses through binding VDR. Vitamin D also changes the balance between Th1 to Th2 and T regulatory cells [38]. Inhibiting the proliferation of Th1 cells can induce inflammation, generate bone loss leading to osteopenia or osteoporosis [39]. However, vitamin D decreases acute-phase response rather than causing inflammation [40].

There are some limitations in our study. First, the patient's long-term follow up was not conducted. Second, we did not note clothing, sun exposure and season. Third, we did not measure vitamin D receptors.

In conclusion, this study presents a negative correlation between serum vitamin D level and DAS28. This study concluded that serum vitamin D can be measured as an alternative marker in patients with RA.

Since vitamin D has autoimmune roles, deficiency or inadequacy can cause flaring in patients with RA. In the light of these findings, we recommend vitamin D supplementation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national re-

search committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Scott DL, Steer S. The course of established rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2007; 21: 943-67.
2. Choi SJ, Rho YH, Ji JD, Song GG, Lee YH. Genome scan meta-analysis of rheumatoid arthritis. Rheumatology (Oxford). 2006; 45(2): 166-70.
3. Cantorna MT. Why do T cells express the vitamin D receptor? Ann N Y Acad Sci. 2011; 1217: 77-82.
4. Kamen DL, Aranow C. The link between vitamin D deficiency and systemic lupus erythematosus. Curr Rheumatol Rep. 2008; 10(4): 273-80.
5. Cutolo M, Paolino S, Sulli A, Smith V, Pizzorni C, Seriolo B. Vitamin D, steroid hormones, and autoimmunity. Ann N Y Acad Sci. 2014; 1317: 39-46.
6. Gallone G, Haerty W, Disanto G, Ramagopalan SV, Ponting CP, Berlanga-Taylor AJ. Identification of genetic variants affecting vitamin D receptor binding and associations with autoimmune disease. Hum Mol Genet. 2017. DOI: 10.1093/hmg/ddx092.
7. Vojinovic J, Tincani A, Sulli A, Soldano S, Andreoli L, Dall'Ara F, et al. European multicentre pilot survey to assess vitamin D status in rheumatoid arthritis patients and early development of a new Patient Reported Outcome questionnaire (D-PRO). Autoimmunity Reviews. 2017; DOI:10.1016/j.autrev.2017.03.002
8. Cutolo M, Otsa K, Laas K, Yprus M, Lehtme R, Secchi ME, et al. Vitamin d serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe. Clin Exp Rheumatol. 2006; 24(6): 702-4.
9. Gatenby P, Lucas R, Swaminathan A. Vitamin D deficiency and risk for rheumatic diseases: an update. Curr Opin Rheumatol. 2013; 25(2): 184-91.
10. Feser M, Derber LA, Deane KD, Lezotte DC, Weisman MH, Buckner JH, et al. Plasma 25,OH Vitamin D Concentrations Are Not Associated with Rheumatoid Arthritis (RA)-related Autoantibodies in Individuals at Elevated Risk for RA. The Journal of Rheumatology. 2009; 36 (5): 943-6. DOI: https://doi.org/10.3899/jrheum.080764
11. Grazio S, Naglic DB, Anic B, Naglic DB, Anic B, Bakula M, et al. Vitamin D serum level, disease activity and functional ability in different rheumatic patients. Am J Med Sci. 2015; 349: 46-9.
12 .Brance ML, Brun LR, Lioi S, Sanchez A, Abdala M, Oliveri B. Vitamin D levels and bone mass in rheumatoid arthritis. Rheumatol Int. 2015; 35: 499-505.
13. Sharma R, Saigal R, Goyal L, Mital P, Yadav RN, Meena PD, et al. Estimation of vitamin D levels in rheumatoid arthritis patients and its correlation with the disease activity. J Assoc Physicians India. 2014; 62: 678-81.
14. Hong Q, XU J, Xu S, Lian L, Zhang M, Ding C. Associations between serum 25-hydroxyvitamin D and disease activity, inflammatory cytokines and bone loss in patients with rheumatoid arthritis. Rheumatology (Oxford). 2014; 53: 1994-2001.
15. Chen J, Liu W, Lin Q, Chen L, Yin J, Huang H. Vitamin D deficiency and low bone mineral density in native Chinese rheumatoid arthritis patients. Int J Rheum Dis. 2014; 17: 66-70.
16. Gheita TA, Sayed S, Gheita HA, Kenawy SA. Vitamin D status in rheumatoid arthritis patients: relation to clinical manifestations, disease activity, quality of life and fibromyalgia syndrome. Int J Rheum Dis. 2014; 19(3): 294-9.
17. Sahebari M, Mirfeizi Z, Rezaieyazdi Z, Rafatpanah H, Goshyeshi L. 25(OH) vitamin D serum values and rheumatoid arthritis disease activity (DA S28 ESR). Caspian J Intern Med. 2014; 5: 148-55.
18. Atwa MA, Balata MG, Hussein AM, Abdelrahman NI, Elminshawy HH. Serum 25-hydroxyvitamin D concentration in patients with psoriasis and rheumatoid arthritis and its association with disease activity and serum tumor necrosis factor-alpha. Saudi Med J. 2013; 34: 806-13.
19. Yazmalar L, Ediz L, Alpayci M, Hiz O, Toprak M, Tekeoglu I. Seasonal disease activity and serum vitamin D levels in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis. Afr Health Sci. 2013; 13: 47-55.
20. Baykal T, Senel K, Alp F, Erdal A, Ugur M. Is there an association between serum 25-hydroxyvitamin D concentrations and disease activity in rheumatoid arthritis? Bratisl Lek Listy. 2012; 113: 610-1.
21. Kostoglou-Athanassiou I, Athanassıou P, Lyraki A, Raftakis I, Antoniadis C. Vitamin D and rheumatoid arthritis. Ther Adv Endocrinol Metab. 2012; 3: 181-7.
22. Attar SM. Vitamin D deficiency in rheumatoid arthritis. Prevalence and association with disease activity in Western Saudi Arabia. Saudi Med J. 2012; 33: 520-5.
23. Cutolo M, Otsa K, Laas K, Prus M, Lehtme R, Secchi ME, et al. Circannual vitamin D serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe. Clin Exp Rheumatol. 2006; 24: 702-4.
24. Wen HY, Luo J, Lı XF. Vitamin D levels and associations with disease activity in Chinese Han patients with early rheumatoid arthritis. J Clin Rheumat. 2015; 21: 276-7.
25. Turhanoğlu AD, Güler H, Yönden Z, Aslan F, Mansuroglu A, Ozer C. The relationship between vitamin D and disease activity and functional health status in rheumatoid arthritis. Rheumatol Int. 2011; 31(7): 911-14.
26. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol. 2005; 23: 93–9.
27. Solymossy C, Dixey J, Utley M, Gallivan S, Young A, Cox N, et al. Larsen scoring of digitized X-ray images. Rheumatology. 1999; 38(11): 1127-9.
28. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress and documentation. J Rheumatol. 2003; 30: 167-78.
29. De Jong Z, van der Heijde D, McKenna SP, Whalley D. The reliability and construct validity of the RAQoL: a rheumatoid arthritis-specific quality of life instrument. Br J Rheumatol. 1997; 36: 878–83.
30. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2001; 96: 1911–30.
31. Hajjaj-Hassouni N, Mawani N, Allali F, Rkain H, Hassouni K, Hmamouchi I, et al. Evaluation of Vitamin D Status in Rheumatoid Arthritis and Its Association with Disease Activity across 15 Countries: "The COMORA Study". International Journal of Rheumatology. 2017. DOI: /10.1155/2017/5491676
32. Baker JF, Baker DG, Toedter G, Shults J, Von Feldt JM, Leonard MB. Associations between vitamin D, disease activity, and clinical response to therapy in rheumatoid arthritis. Clin Exp Rheumatol. 2012; 30 (5): 658–64.
33. Salesi M, Farajzadegan Z. Efficacy of Vitamin D in patients with active rheumatoid arthritis receiving methotrexate therapy. Rheumatology international. 2012; 32(7): 2129-33.
34. Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis. The Journal of nutrition. 1998; 128(1):68–72.
35. Adorini L. Intervention in autoimmunity: the potential of vitamin D receptor agonists. Cellular immunology. 2005; 233(2):115–24. DOI: 10.1016/j.cellimm.
36. Tizaoui K, Hamzaoui K. Association between VDR polymorphisms and rheumatoid arthritis disease: Systematic review and updated meta-analysis of case-control studies. Immunobiology. 2014. doi: 10. 1016/j.imbio.2014.12.013 37. Ceglia L, Niramitmahapanya S, da Silva Morais M, Rivas DA, Harris SS, Bischoff-Ferrari H, et al. A randomized study on the effect of vitamin D(3) supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. The Journal of clinical endocrinology and metabolism. 2013; 98(12): DOI: 10.1210/jc.2013-282038. Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. Joint, bone, spine: revue du rhumatisme. 2010; 77(6):552–7. DOI: 10.1016/j.jbspin.39. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Annals of the rheumatic diseases. 2007; 66(9):1137–42.
40. Reid D, Toole BJ, Knox S, Talwar D, Harten J, O'Reilly DS, et al. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. The American journal of clinical nutrition. 2011; 93(5): 1006–11. DOI: 10.3945/ajcn.110.

How to cite this article:
Şaş S, Koçak FA, Kurt EE, Erdem HR, Tuncay F. Vitamin D status and association with disease activity and quality of life in patients with rheumatoid arthritis. Ann Clin Anal Med 2019;10(4): 462-5.